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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,554	YANG ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 19-21* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/28/08 has been entered. Applicant's claim amendment and response filed concurrently with the RCE have also been entered. Claims 4-18 are canceled and new claim 21 has been added. Claims 1-3 and 19-21 are currently pending in the instant application. Of these, claims 19-20 remain withdrawn from prosecution as being drawn to subject matter nonelected without traverse. Claims 1-3 and 21 are therefore under consideration. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Applicant's amendment has necessitated the following new grounds of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 21 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The applicant has amended claim 1 to recite that the transgenic rodent is obtained by crossing a rodent comprising a transgenic expression system comprising a nucleotide sequence encoding a fluorescent protein operatively linked to a promoter "that is active in all cells of said rodent" with an immunocompromised rodent. The phrase, "that is active in all cells of said rodent" is confusing as the preamble identifies the rodent as not expressing the fluorescent protein in erythrocytes. Since erythrocytes are cells, the added limitation appears to conflict with the preamble such that the metes and bounds of the claim cannot be determined. Claims 2-3 and 21 depend on claim 1 and thus are included in this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 21 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The applicant has amended claim 1 to recite that the transgenic rodent is obtained by crossing a rodent comprising a transgenic expression system comprising a nucleotide sequence encoding a fluorescent protein operatively linked to "a promoter that is active in all cells of said rodent" with an immunocompromised rodent. However, the specification fails to provide

adequate written description for the genus of promoters that are "active in all cells" of a rodent. The specification does not refer to a genus of promoters. Instead, the disclosure of the specification in regards to the claimed subject matter is limited to a description of transgenic mice previously made by Okabe et al. (1997) FEBS Lett., Vol. 467, 313-319 (of record). On page 2, the specification discloses the Okabe paper and teaches that the authors utilized a chicken beta-actin promoter and cytomegalovirus enhancer to express GFP in the entire body. Page 10 of the specification discloses the use of these exact mice to make immunocompromised nu/nu GFP expressing mice, where GFP expression is under control of the beta-actin promoter and cytomegalovirus enhancer. These are the only references to a promoter or any type of transcriptional regulatory sequence in the entire specification. Furthermore, it is noted that the beta-actin promoter and cytomegalovirus enhancer does not drive expression of GFP in "all cells" as the specification clearly teaches that GFP expression is not observed in erythrocytes. Therefore, the specification's disclosure is limited to a description of a single species of promoter, the beta-actin promoter, and does not provide the requisite support for the added limitation of a genus of promoters capable of expressing GFP in all cells of a rodent. While it is noted that the specification does generically refer to rodents which express GFP in "essentially all tissues" or the "majority of tissues", this is not the same as the currently claimed limitation of expression in "all cells". Further, it is noted that disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Therefore, for the reasons set forth above, the added limitation is considered new matter not supported by the as filed specification.

Claim Rejections - 35 USC § 102

The rejection of claims 1-3 under 35 U.S.C. 102(a) as being anticipated by WO 02/28188 A1 (4/1/02), hereafter referred to as Kern, is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

It is first noted that the claims as amended are confusing as the added limitation that the promoter is active in "all cells" conflicts with the preamble limitation that the fluorescent protein is not expressed in erythrocytes. In the interests of compact prosecution, the claim has been interpreted to be drawn to the use of a promoter which expresses the fluorescent protein in all cells with a nucleus.

The applicant argues that Kern et al. does not anticipate the instant invention because 1) Kern does not specifically teach that all tissues of the described transgenic mouse express GFP, 2) Kern does not provide adequate guidance for making a transgenic mouse as claimed, 2) Kern did not have the same reasons for making the mouse as the inventors, and 4) that since Kern teaches a "constitutive" promoter, it would not be "inevitable" that GFP is expressed in all tissues.

In response, it is first noted that applicant's statement that the purpose of the creation of the transgenic animals of Kern is different from that of inventors is not compelling as the use of the immunocompromised GFP expressing mice to study transplanted tumors is clearly taught by applicants on for example page 3. Thus, Kern's reasons for creating an immunocompromised GFP expressing mouse is that same as applicants. However, more importantly, the "reasons" why

Kern may have wanted to create such a mouse are irrelevant to the patentability of the claims under 35 USC 102 since Kern teaches to make a product with the same structure as that claimed by applicant.

Regarding applicant's argument that Kern et al. does not provide enough guidance for making a mouse as claimed, this is not agreed. Kern et al. on pages 10-11 teaches methods of making the mouse by stably integrating the detectable gene into the chromosome of a mouse embryonic stem cell and using the embryonic cell to develop strains of homozygous mice having two copies of the integrated construct in every cell, and then breeding the mice with nu/nu mice to produce mice that are homozygous for the transgene and homozygous for immunodeficiency. The guidance provided by Kern is in fact more detailed than that provided by the instant specification for making transgenic mice.

Regarding the argument that Kern does not specifically teach that all tissues of the described transgenic mouse express GFP and that since Kern teaches a "constitutive" promoter, it would not be "inevitable" that GFP is expressed in all tissues since a constitutive promoter could encompass a tissue specific promoter, the applicant is first reminded that "[w]hen the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). Kern clearly teaches to use a constitutive promoter and further teaches on page 13, "[t]his may be the case, for example, when the selectable trait is constitutive and is detectably expressed in the cells of the transgenic animal. [f]or example, if the selectable trait is the constitutive expression of GFP….". From this passage, it is clear that Kern is not contemplating tissue specific, but global GFP expression. Nowhere does Kern teach to use a tissue-specific

promoter. In addition, as noted in the previous office action, applicant's responses provide a definition for "constitutive" promoter that is unsupported by any prior art reference. Further, even if *arguendo*, the genus of constitutive promoters included some tissue specific promoters, Kern's teachings are clearly not directed to this alleged subspecies of constitutive promoters, but rather teaches generically to use a constitutive promoter such that any type of transplanted tissue can be later harvested and contaminating recipient cells removed by on the constitutive expression of GFP. Therefore, applicant's arguments are not persuasive in demonstrating that GFP expression in all cells except erythrocytes would not be an inherent property of the mice disclosed by Kern.

It is again reiterated that once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference. MPEP 2112. V, emphasis added. Further, MPEP 2112 states that "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on '*prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Therefore, applicant's arguments are not found persuasive.

Applicant's addition of new claim 21 has necessitated the following new grounds of rejection under 35 USC 103.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 21 rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/28188 A1 (4/1/02), hereafter referred to as Kern, in view of Okabe et al. (1997) FEBS Lett., Vol. 467, 313-319.

Please note that the claims are product by process claims. The applicant is reminded that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

Kern teaches a transgenic immunodeficient organism which exhibits a detectable trait such as the expression of a detectable marker (Kern, page 4). Kern specifically teaches that the

organism is a transgenic mouse, and more specifically the offspring of a nu/nu mouse, which expresses the detectable marker green fluorescent protein (Kern, page 4, and page 23, claims 18-24). Kern further teaches methods of making the mouse by stably integrating the detectable gene into the chromosome of a mouse embryonic stem cell and using the embryonic cell to develop strains of homozygous mice having two copies of the integrated construct in every cell, and then breeding the mice with nu/nu mice to produce mice that are homozygous for the transgene and homozygous for immunodeficiency (Kern, pages 10-11). Kern further teaches the constitutive expression of green fluorescent protein in the nu/nu mice (Kern, pages 13). Note in particular that Kern et al. teaches breeding the mouse transgenic for the selectable trait, such as constitutive GFP expression, to heterozygosity or homozygosity, where the transgene is integrated into the chromosomes of every cell in the mouse, and then cross-breeding that strain to a nu/nu mouse strain to create a homozygous GFP+/GFP+:nu/nu mouse or a heterozygous GFP+/-:nu/nu mouse (Kern, pages 10-11, bridging paragraph).

Kern differs from the instant invention by not teaching the use of the beta-actin promoter to constitutively express GFP in the immunodeficient transgenic mice. Okabe et al. supplements the teachings of Kern by teaching the production of a transgenic mouse comprising a transgene encoding GFP under control of the chicken beta-actin promoter (Okabe et al., page 313). Okabe et al. further teaches that GFP was expressed in all tissues of the mouse with the exception of erythrocytes and hair (Okabe et al., page 313). Based on the specific motivation provided by Kern for breeding a transgenic mouse constitutively expressing GFP with an immunodeficient nu/nu mouse to produce a homozygous GFP+/GFP+:nu/nu mouse, it would have been *prima facie* obvious to the skilled artisan at the time of filing to breed the GFP transgenic mouse of

Okabe et al., where GFP is under transcriptional control of the constitutive beta-actin promoter, with a nu/nu mouse as taught by Kern to produce an immunodeficient transgenic mouse which expresses GFP in all tissues except hair and erythrocytes. Further, based on the well developed techniques of breeding mice at the time of filing, the specific guidance provided by Kern for breeding GFP transgenic mice with nu/nu mice and the detailed guidance provided by Okabe et al. for making a transgenic mouse encoding GFP under control of a beta-actin promoter, the skilled artisan would have had a reasonable expectation of success in making an immunodeficient transgenic mouse as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197.

Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633